Liver Adaptation to Xenobiotic Injury

Tacrine, isoniazid, alcohol, ximelagatran: development of clinical tolerance

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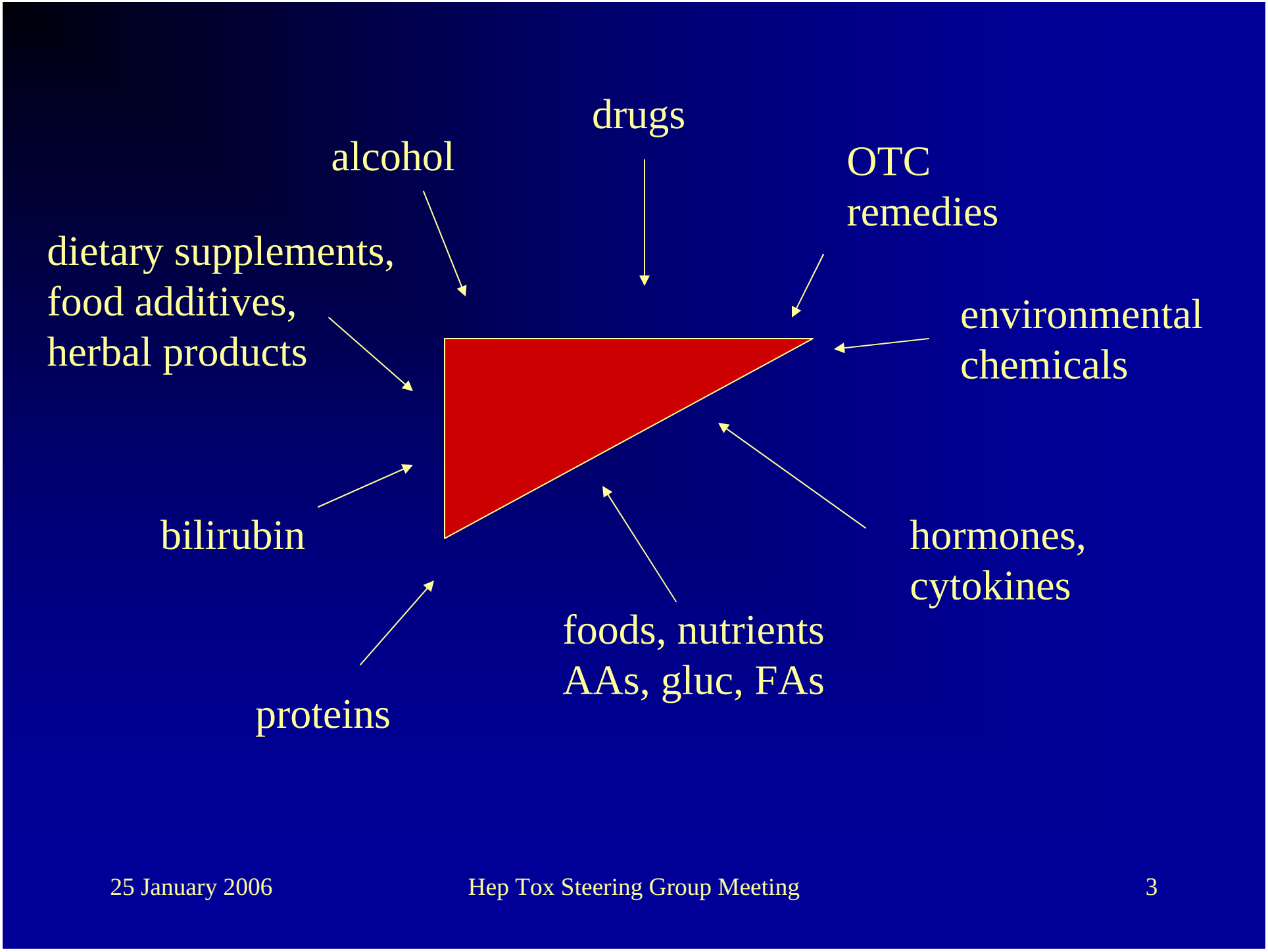
Material presented here is based on the observations of the speaker for 20 years in academic hepatology and gastroenterology, 5 years as a senior executive in the pharmaceutical industry, 11 years in private consulting to industry, and upon 10.5 years at the FDA: 4.5 years as a medical reviewer for new gastrointestinal drugs, 3 as the Senior Scientific Advisor for hepatology in the Office of Drug Safety, 3 years as Associate Director for Science, Office of Pharmacoepidemiology and Statistical Science.

Comments made here do not reflect official policies or positions of the Agency, but are personal opinions of the presenter based on his diverse experiences mentioned.


drugs
alcohol
OTC
remedies
dietary supplements,
food additives,
herbal products
environmental
chemicals
bilirubin
hormones,
cytokines
foods, nutrients
AAs, gluc, FAs
proteins

Some Types of Liver Injury

[Drug-Induced Liver Injury Network, DILIN]

Hepatocellular - isoniazid

Cholestatic, intrahepatic - Augmentin

Hypersensitivity, immunologic - phenytoin

Mitochondrial - valproic acid

Early Detection of Hepatotoxicity

1) injury - elevating ALT/AST, AP/GGT
2) early dysfunction - anicteric bilirubin rise
   - slight PT increase
3) dysfunction - jaundice, coagulopathy
   - subclinical encephalopathy

(Serial measures over time! Note changes in the individual, time-rate of change of sensitive measures: ALT, bili, PT)

Drug-Induced Liver Injury (DILI)

Most people exposed to a new drug show no injury;

"tolerators"

Some people show transient injury, but adapt;

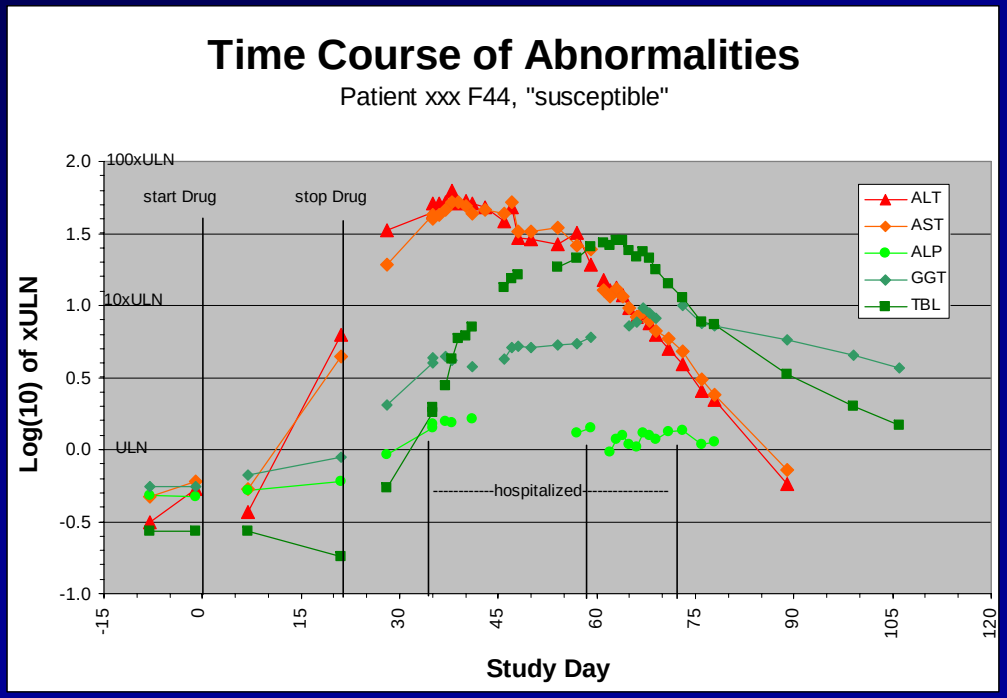
"adaptors"

A few fail to adapt and show serious toxicity !

"susceptibles"

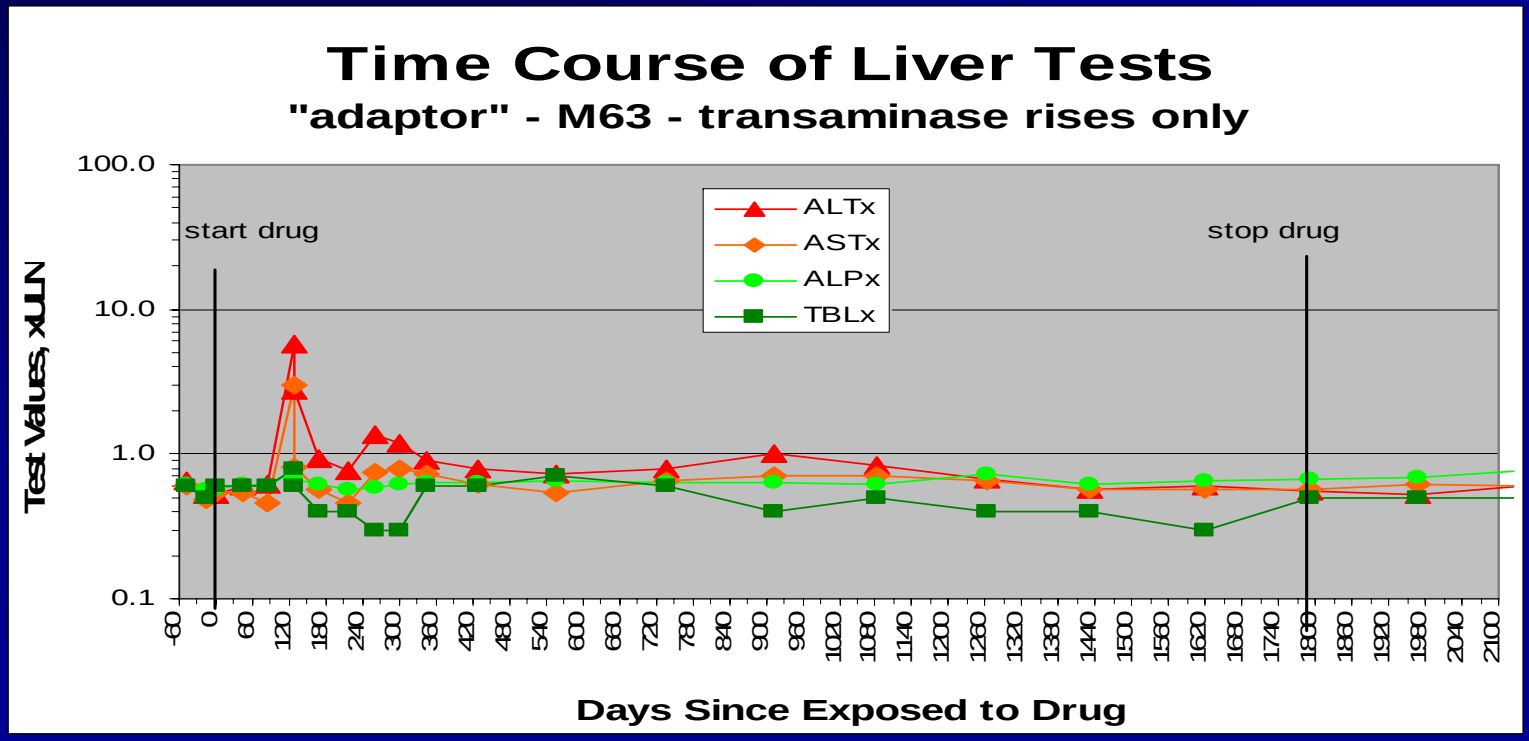
Drug-Induced Liver Injury (DILI)

“susceptibles”



Drug-Induced Liver Injury (DILI)

“adaptors”



Tip of the Iceberg

Death or Tx

Acute Liver Failure

Serious DILI – Threatening

Detectable DILI – but Not Serious

Patient Adaptation to New Agent Exposure

Patients/People Tolerate Exposure Without Effects

Why Are They Susceptible ?

"idio-sug-krasia" (Hippocrates, ~ 400 B.C.)

idios (ιδιος) - one's own, self

syn (συν) - together

crasis (κρασις) - mixing, mixture

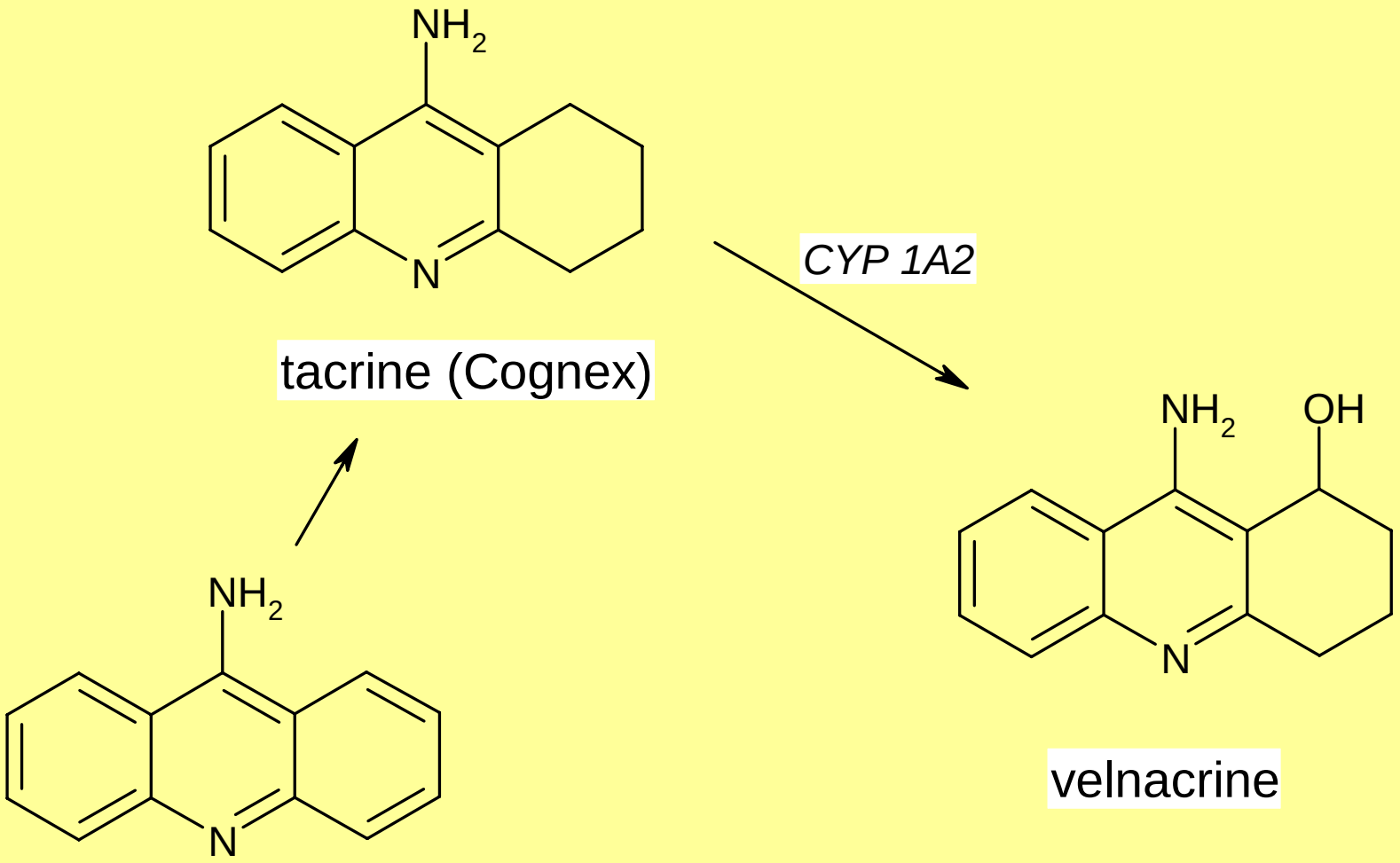
therefore,

a person's own individual mixture of characteristics, factors; "nature and nurture," unique in the world

[it does NOT mean rare, unexpected, unexplained, although it may or may not be any or all of them]

Factors in Idiosyncrasy

- **genetic, bestowed at conception**
  - –gender
  - –cytochromes, enzymes, transport systems
- **acquired in life since conception**
  - –age, activities, travels
  - –infections, immunities, diseases
  - –diet, obesity, dietary supplements
  - –other drugs, chemical exposures
- ***differences in resistance, repair, healing !!***


NH2
N
tacrine (Cognex)
CYP 1A2
NH2
OH
N
velnacrine
NH2
N
aminacrine

Tacrine (Cognex®)

cholinesterase inhibitor used to treat Alzheimer's Disease

(Approved September 1993, with weekly ALT monitoring)

Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW. Hepatotoxicity effects of tacrine administration in patients with Alzheimer's disease. JAMA 1994; 271:992-8.

Peak ALT elevations in tacrine clinical trials

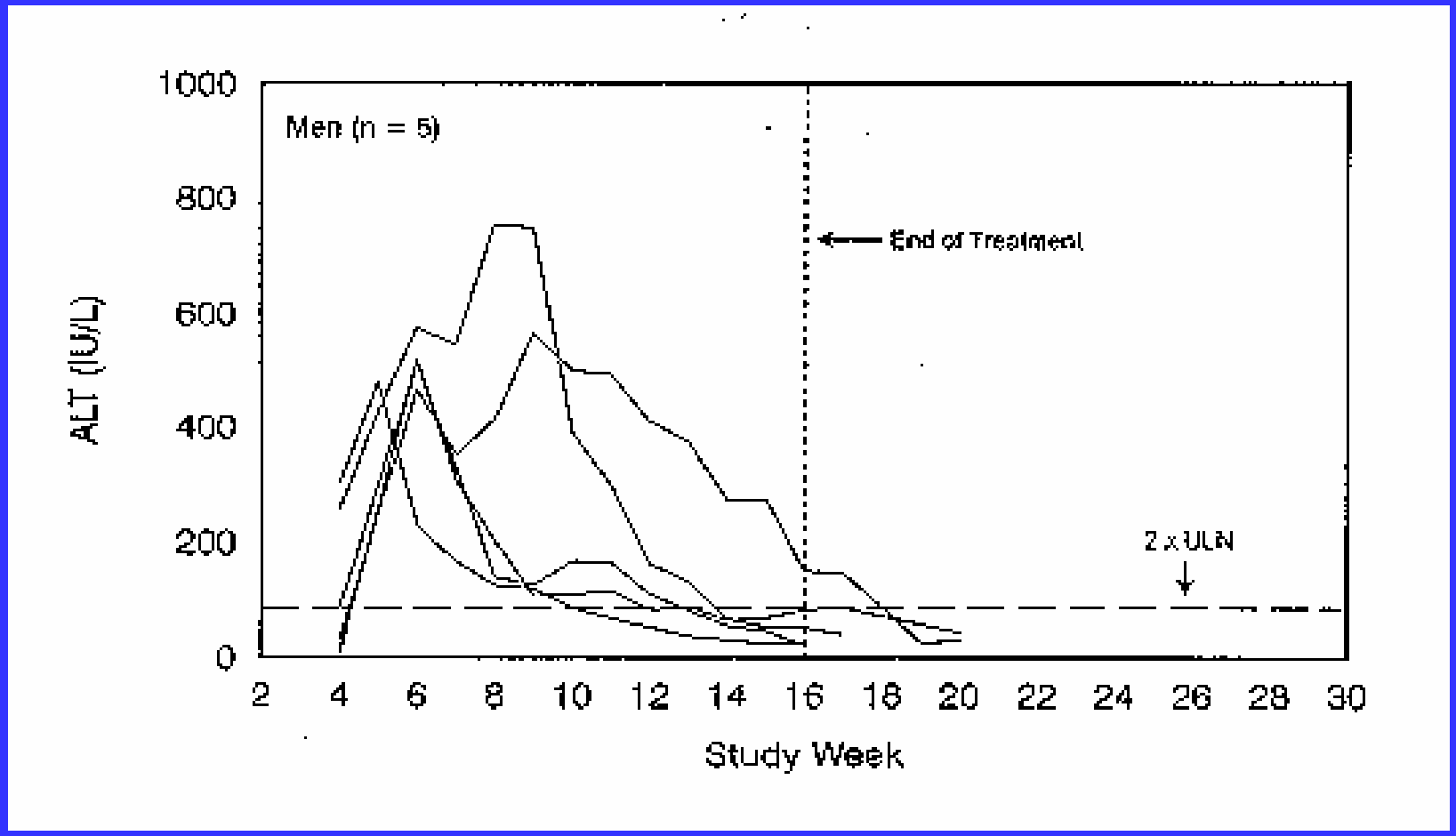
… in 2446 patients (5 studies, US, CA, FR)

> ULN	- 49%
> 2 X ULN	- 32%
> 3 X ULN	- 25%
> 20 X ULN	- 2%

. . . more in women than men,

no deaths, no TBL > 3 mg/dL

Treatment with tacrine through ALT elevations



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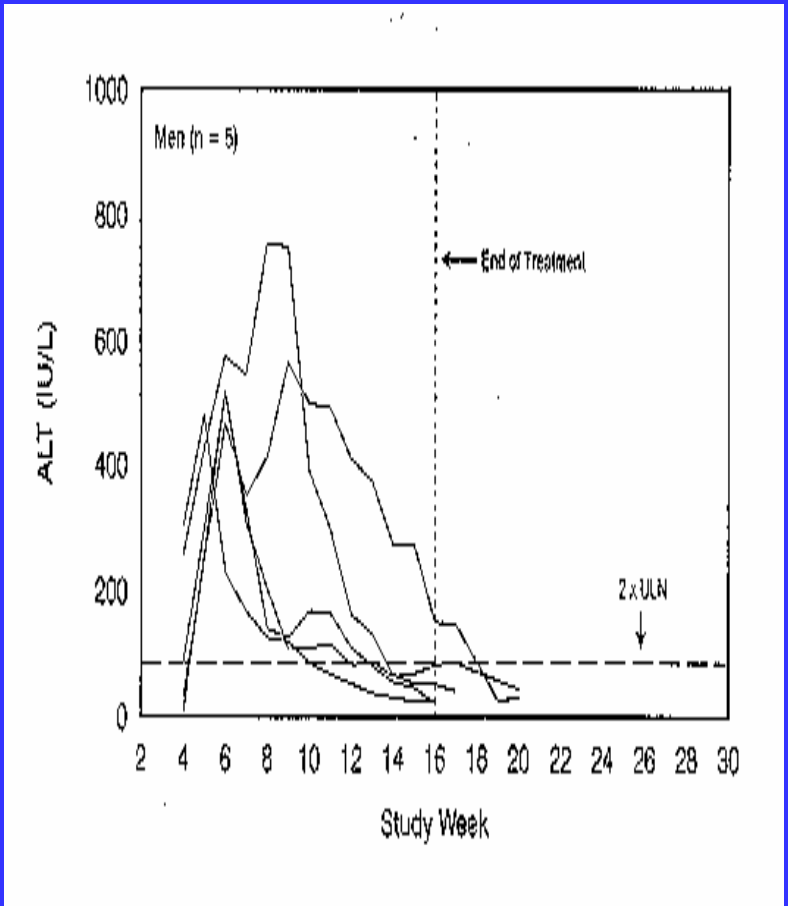
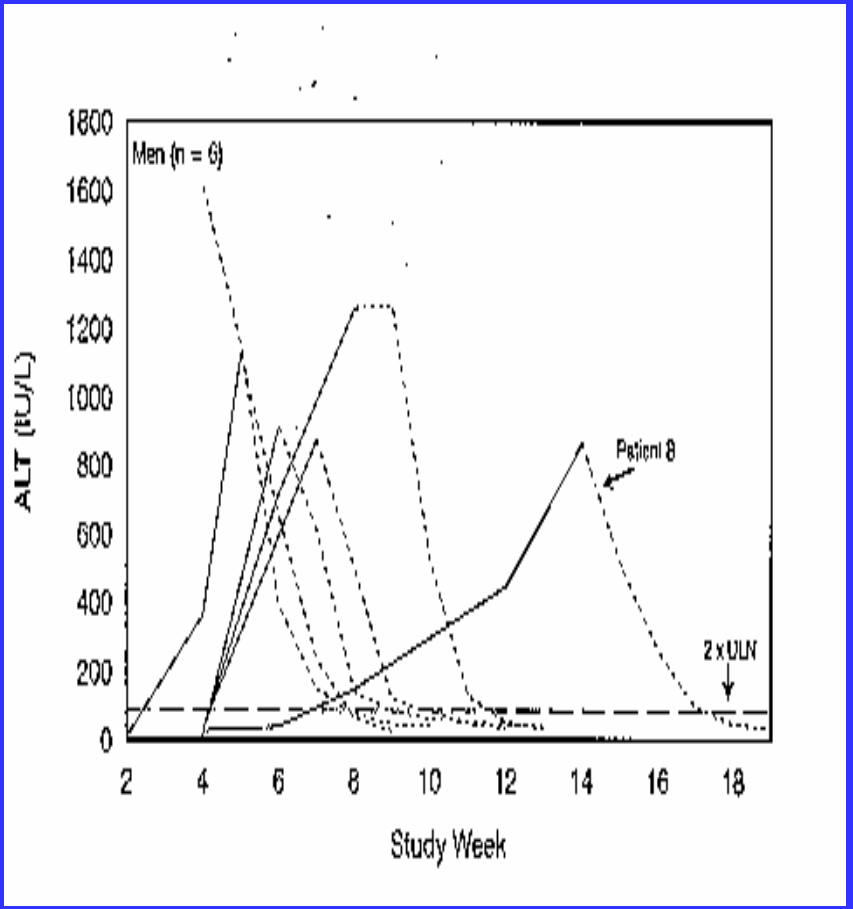
Reversed on treatment Treatment stopped





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Effects of rechallenge

1) Of 212 patients with peak ALT >3 xULN, 145 consented to rechallenge after ALT returned to <2 xULN off tacrine >2-24 weeks

2) Only 48 (33%) showed ALT >3 xULN, but often more rapidly than initially; only 18 (12%) had to quit tacrine permanently

3) Most (97) showed lower ALT on rechallenge than initially, and 90 (72%) resumed tacrine treatment at higher doses than initially

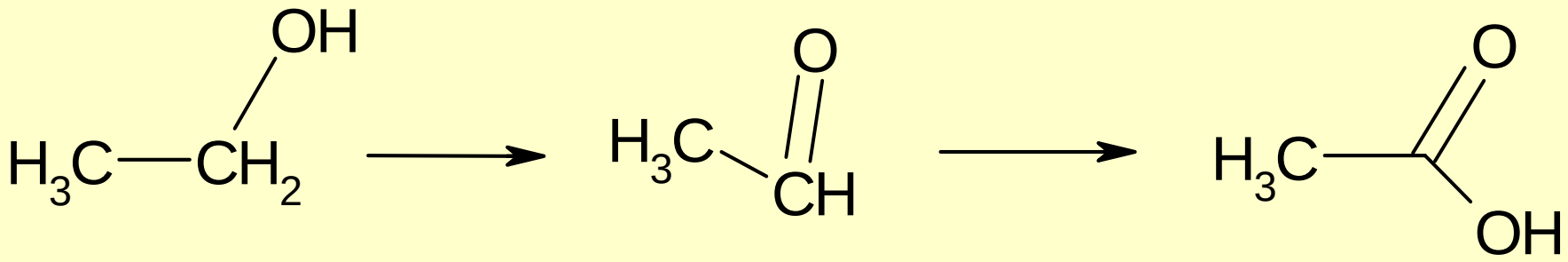
Possible explanations for reversible ALT elevations

1) ALT elevations reversing on treatment have no relationship to those that can progress to liver failure.
2) ALT elevations overestimate true risk
3) Only a subset of those with ALT elevations progress to liver failure.

Rechallenge to a drug that has caused liver injury does not always cause prompt and more severe recurrent injury;

Negative rechallenge response isn't always proof that the drug did not cause original injury!! *(Especially if not an immune response)*

Why? Because of adaptive tolerance. . . (Still to be proved)



ethanol

acetaldehyde

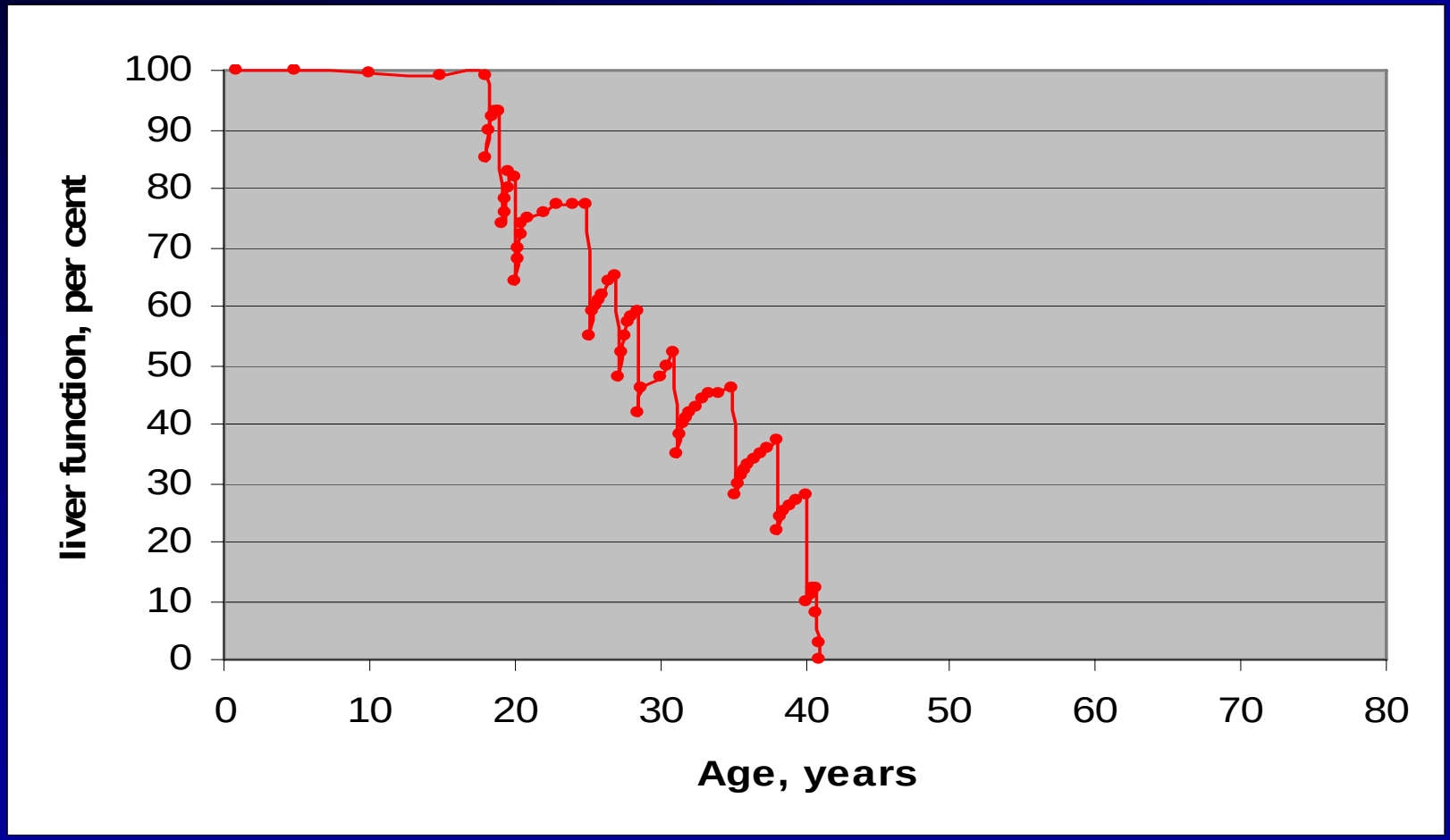
acetate

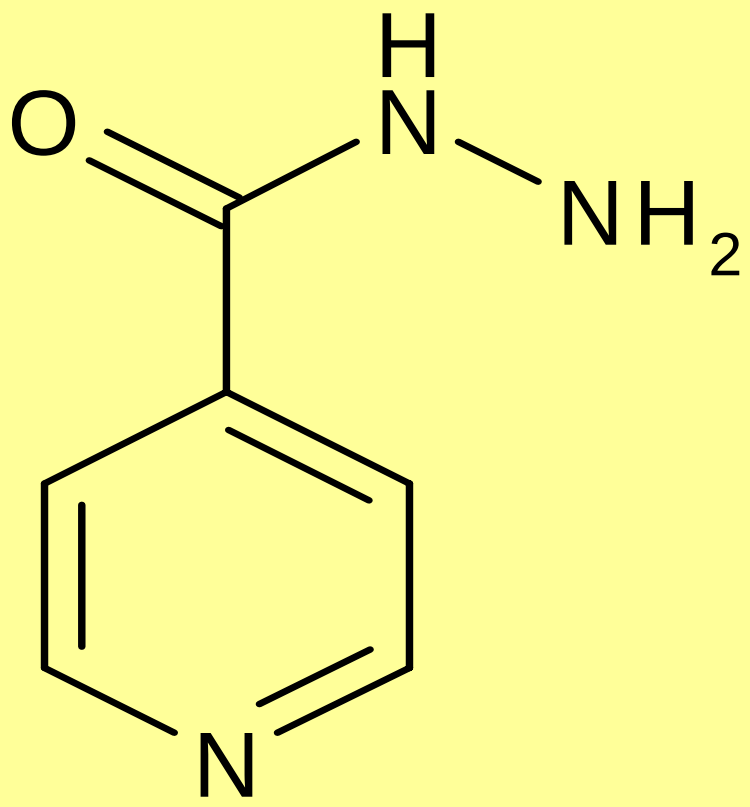
Time Course of Alcoholic Liver Disease

Acute alcoholic hepatitis (Beckett, Livingstone, Hill; 1961):

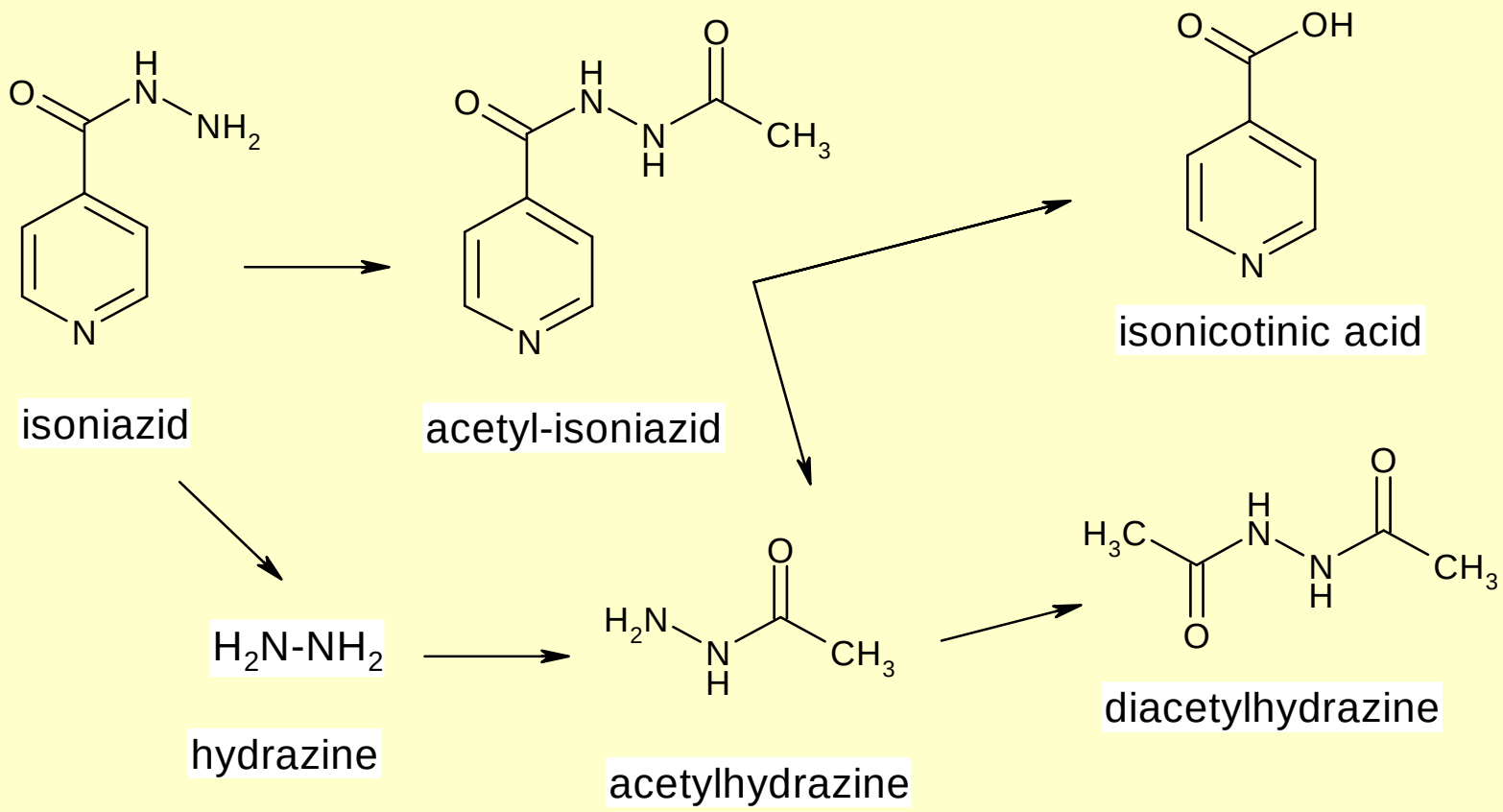
- anorexia, right upper abdominal pain, nausea,
- jaundice, leukocytosis, fever, tender hepatomegaly
- history of recent alcoholic binge
- modest elevation of AST >ALT, INR, ALP
- low platelets, Mg, K, anemia
- centrilobular necrosis, neutrophils, hyaline, fat
- often worsens after alcohol stopped
- fibrosis, cirrhosis depend on previous episodes
- progresses to cirrhosis with repeated bouts
- dose-duration related in susceptibles (<20%)
- if not susceptible, just fatty liver

Time Course of Alcoholic Liver Disease





isoniazid


isoniazid
acetyl-isoniazid
isonicotinic acid
H_2N-NH_2
hydrazine
acetylhydrazine
diacetylhydrazine

Mitchell et al. first thought that fast acetylators were at increased risk, and acetylhydrazine was the toxic intermediate . . .

[But it turned out that slow acetylators were more susceptible, and maybe hydrazine itself was more toxic.]

But they did say **"This raises the possibility that patients who progress to clinical hepatitis have livers that fail to adapt or to develop adequate repair mechanisms to cope with the insult."**
Clin Pharmacol Ther 1975; 18:70-9.

Isoniazid alone, as prophylaxis against tuberculosis, leads to high incidence of transaminase elevations, depending on age of recipients (more with older age).

Most people, however, can tolerate isoniazid chronically, without severe hepatotoxicity.

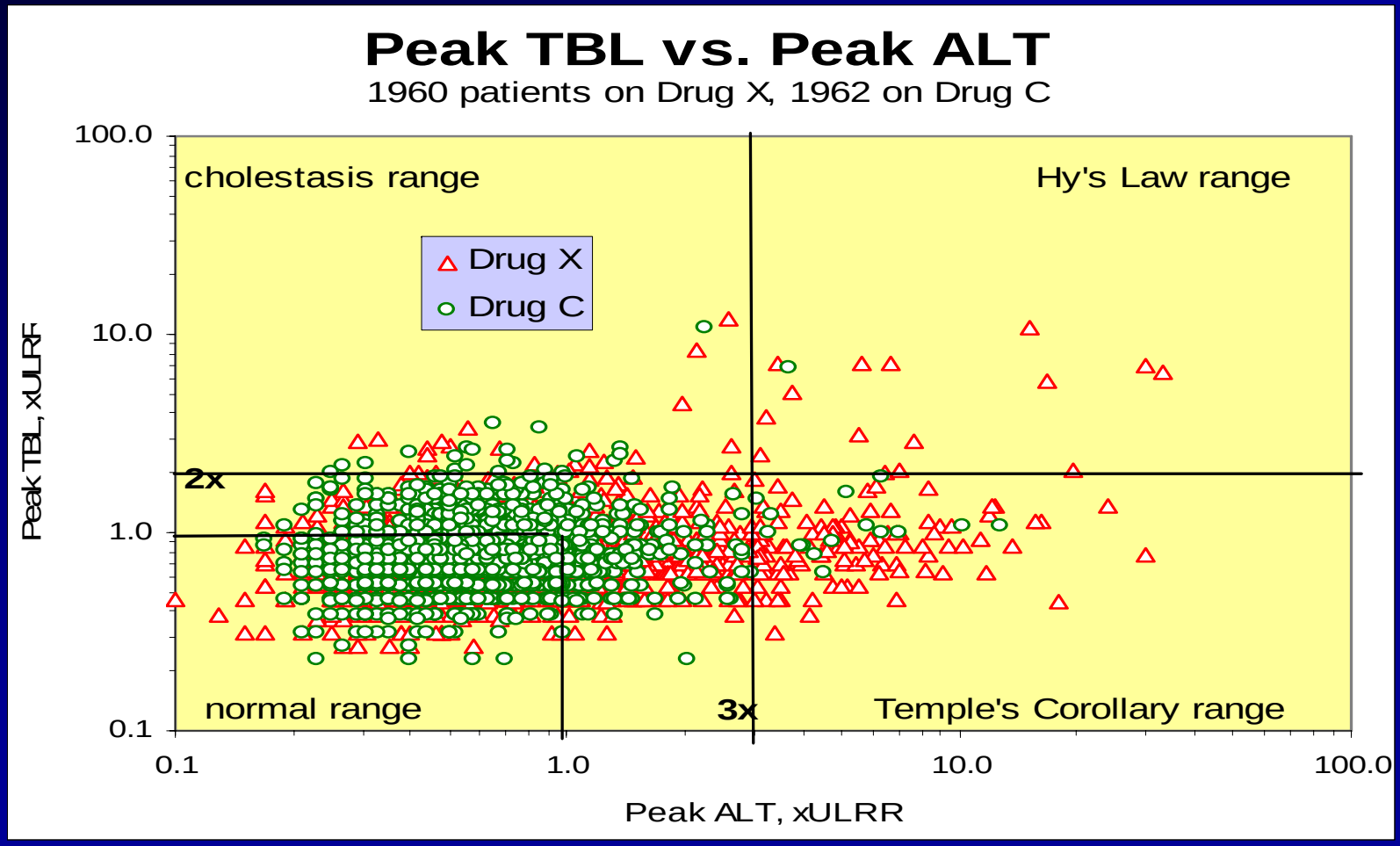
Is screening for transaminase elevations really necessary for preventing serious liver injury?

Despite worrisome incidence of serious liver injury, with 8 deaths in 13,838 persons taking prophylaxis with INH (Kopanoff et al., 1978), a new study of 11,141 patients was done from 1989-1995 by Nolan et al. in Seattle (JAMA 1999; 281:1014-8).

No transaminase monitoring, but patients reminded to report any symptoms at once, stop INH and get checked. No deaths, only 11 (1:1000) had to stop INH permanently. Most adapted to INH.

Why? 1) younger patients (and prompt stopping)
2) lower incidence on symptoms than enzymes

Graphic representation of TBL vs ALT



Hy Zimmerman

1917-1999

He taught us that hepatocellular injury caused by drugs may not be dangerous unless accompanied by liver function loss such as shown by jaundice.

He never wrote about adaptive tolernce to drug-induced injury . . .

Hy said that having some pre-existing liver disease does not necessarily increase likelihood of DILI.

"A stubborn misconception regarding susceptibility to hepatic injury has been the view that patients with preexisting liver disease are more likely than others to experience hepatic injury on exposure to drugs that cause liver damage."

He never clarified whether the disease might make recovery from the injury harder. . .

"Nevertheless, it seems clear that the addition of drug-induced hepatic injury to chronic liver disease would be troublesome."

It is not enough to detect liver injury that has aleady occurred . . .

We need to learn how to predict liver injury that is likely to occur in certain people, and avoid exposing them to the injurious agent and prevent injury!

Or avoid patients who can't adapt!